

GOODMAN & GILMAN's The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Tenth Edition

McGraw-Hill
MEDICAL PUBLISHING DIVISION

New York	Chicago	San Francisco	Lisbon	London	Madrid	Mexico City
Milan	New Delhi	San Juan	Seoul	Singapore	Sydney	Toronto

BEST AVAILABLE COPY

10. AUG. 2005 10:18 LUDERSCHMIDT & PARTNER 11. 342 5. 37 14

EDITORS

Joel G. Hardman, Ph.D.

Professor of Pharmacology, Emeritus
Vanderbilt University Medical Center
Nashville, Tennessee

Lee E. Limbird, Ph.D.

Professor of Pharmacology
Associate Vice Chancellor for Research
Vanderbilt University Medical Center
Nashville, Tennessee

CONSULTING EDITOR

Alfred Goodman Gilman, M.D., Ph.D., D.Sc. (Hon.)

Raymond and Ellen Willie Distinguished Chair in Molecular Neuropharmacology
Regental Professor and Chairman, Department of Pharmacology
University of Texas Southwestern Medical Center
Dallas, Texas

McGraw-Hill

A Division of The McGraw-Hill Companies



Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS. 10/e

Copyright © 2001, 1996, 1990, 1985, 1980, 1975, 1970, 1965, 1955, 1941 by *The McGraw-Hill Companies, Inc.* All rights reserved. Printed in the United States of America. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a data base or retrieval system, without the prior written permission of the publisher.

1234567890 DOWDOW 0987654321

ISBN 0-07-135469-7

This book was set in Times Roman by York Graphic Services, Inc. The editors were Martin J. Wonsiewicz and John M. Morriss; the production supervisor was Philip Galea; and the cover designer was Marsha Cohen/Parallelogram. The index was prepared by Irving Condé Tullar and Coughlin Indexing Services, Inc. R.R. Donnelley and Sons Company was printer and binder.

This book is printed on acid-free paper.

Library of Congress Cataloging-in-Publication Data

Goodman and Gilman's the pharmacological basis of therapeutics.—10th ed. / [edited by] Joel G. Hardman, Lee E. Limbird, Alfred Goodman Gilman.
p. ; cm.

Includes bibliographical references and index.

ISBN 0-07-135469-7

I. Pharmacology. 2. Chemotherapy. I. Title: Pharmacological basis of therapeutics.
II. Goodman, Louis Sanford III. Gilman, Alfred IV. Hardman, Joel G.
V. Limbird, Lee E. VI. Gilman, Alfred Goodman
[DNLM: 1. Pharmacology. 2. Drug Therapy. QV 4 G6532 2002]

RM300 G644 2001

615'.7—dc21

2001030728

INTERNATIONAL EDITION ISBN 0-07-112432-2

Copyright © 2001. Exclusive rights by *The McGraw-Hill Companies, Inc.*, for manufacture and export. This book cannot be re-exported from the country to which it is consigned by McGraw-Hill. The International Edition is not available in North America.

BEST AVAILABLE COPY

tone is low (Marshall *et al.*, 1987; Hanel and Lands, 1982). Further, acetaminophen does not inhibit neutrophil activation as do other NSAIDs (Abramson and Weisemann, 1989).

Single or repeated therapeutic doses of acetaminophen have no effect on the cardiovascular and respiratory systems. Acid-base changes do not occur, nor does the drug produce the gastric irritation, erosion, or bleeding that may occur after administration of salicylates. Acetaminophen has no effects on platelets, bleeding time, or the excretion of uric acid.

Pharmacokinetics and Metabolism. Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes, and the half-life in plasma is about 2 hours after therapeutic doses. Acetaminophen is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; only 20% to 50% may be bound at the concentrations encountered during acute intoxication. After therapeutic doses, 90% to 100% of the drug may be recovered in the urine within the first day, primarily after hepatic conjugation with glucuronic acid (about 60%), sulfuric acid (about 35%), or cysteine (about 3%); small amounts of hydroxylated and deacetylated metabolites also have been detected. Children have less capacity for glucuronidation of the drug than do adults. A small proportion of acetaminophen undergoes cytochrome P450-mediated *N*-hydroxylation to form *N*-acetyl-benzoquinoneimine, a highly reactive intermediate. This metabolite normally reacts with sulfhydryl groups in glutathione. However, after ingestion of large doses of acetaminophen, the metabolite is formed in amounts sufficient to deplete hepatic glutathione (see below).

Therapeutic Uses. Acetaminophen is a suitable substitute for aspirin for analgesic or antipyretic uses; it is particularly valuable for patients in whom aspirin is contraindicated (e.g., those with peptic ulcer) or when the prolongation of bleeding time caused by aspirin would be a disadvantage. The conventional oral dose of acetaminophen is 325 to 1000 mg (650 mg rectally); the total daily dose should not exceed 4000 mg. For children, the single dose is 40 to 480 mg, depending upon age and weight; no more than five doses should be administered in 24 hours. A dose of 10 mg/kg also may be used.

Toxic Effects. In recommended therapeutic dosage, acetaminophen usually is well tolerated. Skin rash and other allergic reactions occur occasionally. The rash is usually erythematous or urticarial, but sometimes it is more serious and may be accompanied by drug fever and mucosal lesions. Patients who show hypersensitivity reactions to the salicylates only rarely exhibit sensitivity to acetaminophen. In a few isolated cases, the use of acetaminophen has been associated with neutropenia, thrombocytopenia, and pancytopenia.

The most serious adverse effect of acute overdosage of acetaminophen is a dose-dependent, potentially fatal hepatic necrosis (see Thomas, 1993). Renal tubular necrosis and hypoglycemic coma also may occur. The mechanism by which overdosage with acetaminophen leads to hepatocellular injury and death involves its conversion to a toxic reactive metabolite (see also Chapter 4). Minor pathways of acetaminophen elimination are via conjugation with glucuronide and sulfate. The major pathway of metabolism is via cytochrome P450s to the intermediate, *N*-acetyl-*para*-benzoquinoneimine, which is very elec-

trophilic. Under normal circumstances, this intermediate is inactivated by conjugation with glutathione (GSH) and then metabolized to a mercapturic acid and excreted into the urine. However, in the setting of acetaminophen overdosage, hepatic levels of GSH become depleted. Two consequences result: depletion of GSH. Since GSH is an important component in antioxidant defense, hepatocytes are rendered highly vulnerable to oxidant injury. Depletion of GSH also allows the intermediate to bind covalently to cell macromolecules, leading to dysfunction of enzymatic systems.

Hepatotoxicity. In adults, hepatotoxicity may occur after ingestion of a single dose of 10 to 15 g (150 to 250 mg/kg of acetaminophen); doses of 20 to 25 g or more are potentially fatal. Alcoholics can have hepatotoxicity with much lower doses, even with doses in the therapeutic range. The mechanism of this effect is discussed above (see also Chapter 4). Symptoms that occur during the first 2 days of acute poisoning with acetaminophen may not reflect the potential seriousness of the intoxication. Nausea, vomiting, anorexia, diaphoresis, and abdominal pain occur during the initial 24 hours and may persist for a week or more. Clinical indications of hepatic damage are manifest within 2 to 4 days of ingestion of toxic doses; aminotransferases are elevated (sometimes markedly), and the concentration of bilirubin in plasma may be increased. In addition, the prothrombin time is prolonged. Perhaps the most serious complication is severe liver damage; of these, 10% to 20% eventually develop hepatic failure. Acute renal failure also occurs in some patients. Biopsy of the liver reveals centrilobular necrosis with involvement of the periportal area. In nonfatal cases, the hepatic lesion is reversible over a period of weeks or months.

Severe liver damage (with levels of aspartate aminotransferase activity in excess of 1000 IU per liter of plasma) occurs in 90% of patients with plasma concentrations of acetaminophen greater than 300 µg/ml at 4 hours or 45 µg/ml at 15 hours after the ingestion of the drug. Minimal hepatic damage is anticipated when the drug concentration is less than 120 µg/ml at 4 hours or 30 µg/ml at 12 hours after ingestion. The potential severity of hepatic necrosis also can be predicted from the half-life of acetaminophen observed in the patient; greater than 4 hours imply that necrosis will occur, while greater than 12 hours suggest that hepatic coma is likely. A nomogram provided in Figure 27-2 relates the plasma level of acetaminophen and time after ingestion to the predicted extent of liver injury (see Rumack *et al.*, 1981).

Early diagnosis is vital in the treatment of overdosage with acetaminophen, and methods are available for the rapid determination of concentrations of the drug in plasma. However, treatment should not be delayed while awaiting laboratory results. If the clinical history suggests a significant overdosage, vigorous supportive therapy is essential when intoxication is severe. Gastric lavage should be performed in all cases, preferably within 4 hours of the ingestion.

The principal antidotal treatment is the administration of sulfhydryl compounds, which probably act, in part, by replenishing hepatic stores of glutathione. *N*-acetylcysteine (MUCOSIL) is effective when given orally or intravenously. The intravenous form is available in Europe, where it is considered the treatment of choice. When given orally, the *N*-acetylcysteine solution (which has a foul smell and taste) is diluted with

Table A-II-1
PHARMACOKINETIC DATA

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE (ml · min ⁻¹ · kg ⁻¹)	VOL. DIST. (liters/kg)	HALF-LIFE (hours)	PEAK TOB (hours)	PEAK CONCENTRATIONS
ABACAVIR (Chapter 51)							
83 (63-110)	1 (0-4)	—	12.8 (9.3-17.5)	0.84 (0.69-1.03)	LD (0.8-1.3)	Tab: 0.63 (0.4-1.1) ^b Sol: 0.5 (0.5-0.6) ^b	Tab: 2.6 (2.3-2.9) ^b µg/ml ^b Sol: 2.9 (2.5-3.4) µg/ml ^b
<p>^aData from male subjects with HIV infection. Values are geometric means and 95% CI. Metabolized by ADH, UGT, and other enzymes.</p> <p>^bC₀ and T_{0.5} (geometric mean and 95% CI) following a 300-mg oral tablet (Tab) or solution (Sol).</p>							
<p>Reference: Barry, M., Makenzie, E., Merry, C., Gibbons, S., and Beck, D. Pharmacokinetics and potential interactions amongst antiretroviral agents used to treat patients with HIV infection. <i>Clin. Pharmacokinet.</i> 1999, 36:289-304.</p> <p>Child, G.E., Gillotin, C., McDowell, J.A., Lou, Y., Edwards, K.D., Prince, W.T., and Stein, D.S. Abacavir: absolute bioavailability, bioequivalence of three oral formulations, and effect of food. <i>Pharmaceuticals</i> 1999, 19:932-942.</p>							
ACETAMINOPHEN (Chapter 27)							
88 ± 15 ↔ Child	3 ± 1 ↔ Neo, Child	<20	5.0 ± 1.4 ^b ↔ Hep ^c ↔ Aged, Child ↔ Obes, HTN, Preg	0.95 ± 0.12 ^b ↔ Aged, Hep ^c LTH, HTN, Child	2.0 ± 0.4 ↔ RD, Obes, Child ↔ Neo, Hep ^c ↔ HTN, Preg	0.33-1.4 ^d	20 µg/ml ^e
<p>^aValues reported are for a linear kinetic model for doses less than 2 g; drug exhibits concentration-dependent kinetics above this dose.</p> <p>^bAssuming a 70-kg body weight; reported range, 65 to 72 kg.</p> <p>^cAcetaminophen-induced hepatic damage or acute viral hepatitis.</p> <p>^dAbsorption rate, but not extent, depends on gastric emptying; hence, allowed after food as well as in some disease states and concomitant with drugs that cause gastroparesis.</p> <p>^eMean concentration following a 20-mg/kg oral dose. Hepatic toxicity associated with levels >300 µg/ml at 4 hours after an overdose.</p>							
<p>Reference: Forrest, J.A., Clements, J.A., and Prescon, L.F. Clinical pharmacokinetics of paracetamol. <i>Clin. Pharmacokinet.</i> 1982, 7:93-107.</p>							
DL-6-ACETYLMETHADOL (LAAMY) (Chapter 23)							
47 ± 3	6	80	4.93 ± 0.58	7.0	L: 18.5 ± 4.9 NL: 21.9 ± 3.2 DL: 63.8 ± 10.1	L: 2.6 ± 0.2 ^b NL: 3.9 ± 0.7 ^b DL: 3.1 ± 9.6 ^b	L: 63 ± 8 ng/ml ^b NL: 44 ± 4 ng/ml ^b DL: 19 ± 1 ng/ml ^b
<p>^aData from healthy adult male subjects. LAAM (L) is metabolized by cytochrome P450 (primarily CYP3A) to active metabolites, rac-LAAM (NL) and diac-LAAM (DL).</p> <p>^bFollowing a single 40-mg oral dose.</p>							
<p>Reference: Kallo, R.F., Chazotte, N., and Jurek, C.E. Simultaneous determination of racetyl-metabolite and its active biotransformation products in human biofluids. <i>J. Chromatogr.</i> 1974, 109:247-253.</p> <p>Wabbe, S.J., Johnson, R.E., Conn, E.J., and Higley, C.E. Intravenous and oral L-6-acetylmethadol: pharmacokinetics and pharmacodynamics in humans. <i>J. Pharmacol. Exp. Ther.</i> 1988, 235:71-82.</p>							
DL-6-ACETYLMETHADOL (LAAMY) (Chapter 23)							
68 ± 3 ↔ Aged, Ctr	1.4 ± 1.2	49 ↔ RD	9.3 ± 1.1 ↔ Aged, Ctr	0.15 ± 0.03	0.25 ± 0.03 ↔ Hep	0.39 ± 0.21 ^b	24 ± 4 µg/ml ^b
<p>^aValues given are for unchanged parent drug. Acetylmethadol acid is converted to salicylic acid during and after absorption (CL and t_{1/2} of salicylic acid are dose-dependent; half-life varies between 2-3 hours after a 500-mg dose to 15 hours when there is intoxication).</p> <p>^bValues given are for unchanged parent drug.</p>							
<p>Reference: Roberts, M.S., Rumble, R.H., Wanwinotai, S., Thomas, D., and Brooks, P.M. Pharmacokinetics of salicylic acid and salicylic acid in elderly subjects and in patients with alcoholic liver disease. <i>Eur. J. Clin. Pharmacol.</i> 1983, 25:253-261.</p>							

therapy

INFLAMMATORY

to four times

daily

daily

to four

four

four

e daily

een propionic
acids. The sim-
ilarity of the oth-
er than are the

of one or an-
other of the symp-
toms of osteoarthritis,
rheumatoid arthritis;
they also
d bursitis, and
injury. Dosage
is shown in

ic acid deriva-
tives of the signs
of osteoarthritis.
a reduction in
stiffness. By
and stamina
untoward ef-
fects. In the
case of in-
jury, aspirin is
derivatives for

ibuprofen, keto-
profen, and
aspirin. In the
United States,
use or under
aspirin, carpro-
fen, and
propionic acid
is experience

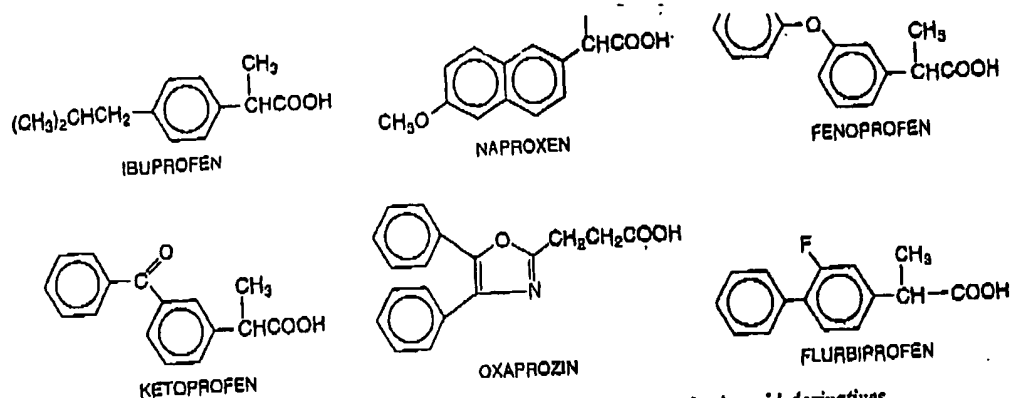


Figure 27-3. Structural formulas of antiinflammatory propionic acid derivatives.

With this drug is greater. It is available for sale without a prescription in the United States. Naproxen has a longer half-life than most of the other structurally and functionally similar agents, making twice-daily administration of it feasible. This drug also is available without a prescription in the United States. Oxaprozin also has a long half-life and can be given once daily. The structural formulas of these drugs are shown in Figure 27-3.

Pharmacological Properties. The pharmacodynamic properties of the propionic acid derivatives do not differ significantly. All are effective cyclooxygenase inhibitors, although there is considerable variation in their potency. For example, naproxen is approximately 20 times more potent than aspirin, while ibuprofen, fenopropfen, and aspirin are roughly equipotent as cyclooxygenase inhibitors. All of these agents alter platelet function and prolong bleeding time, and it should be assumed that any patient who is intolerant of aspirin also will experience a severe reaction after administration of one of these drugs. Some of the propionic acid derivatives have prominent inhibitory effects on leukocyte function; naproxen is particularly potent in this regard. While the compounds do vary in potency, this is not of obvious clinical significance. All are effective antiinflammatory agents in various experimental animal models of inflammation; all have useful antiinflammatory, analgesic, and antipyretic activities in human beings. Although all of these compounds can cause gastric toxicity in patients, these are usually less severe than with aspirin.

It is difficult to find data on which to base a rational choice among the members of the propionic acid derivatives, if in fact one can be made. However, in relatively small clinical studies that compared the activity of several members of this group, patients preferred naproxen in terms of analgesia and relief of morning stiffness (see

Huskisson, in Symposium, 1983a; Hart and Huskisson, 1984). With regard to side effects, naproxen was the best tolerated, followed by ibuprofen and fenopropfen. There was considerable interpatient variation in the preference for a single drug and also between the designations of the best and the worst drug. Unfortunately, it is probably impossible to predict *a priori* which drug will be most suitable for any given individual. Nevertheless, more than 50% of patients with rheumatoid arthritis probably will achieve adequate symptomatic relief from the use of one or another of the propionic acid derivatives, and many clinicians favor their use instead of aspirin in such patients.

Drug Interactions. The potential adverse drug interactions of particular concern with propionic acid derivatives result from their high degree of binding to albumin in plasma. However, the propionic acid derivatives do not alter the effects of the oral hypoglycemic drugs or warfarin. Nevertheless, the physician should be prepared to adjust the dosage of warfarin because these drugs impair platelet function and may cause gastrointestinal lesions.

Ibuprofen

Ibuprofen is supplied as tablets containing 200 to 800 mg; of the 200-mg tablets (ADVIL, NUPRIN, others) are available without a prescription.

For rheumatoid arthritis and osteoarthritis, daily doses up to 3200 mg in divided portions may be given, although usual total dose is 1200 to 1800 mg. It also may be possible to reduce the dosage for maintenance purposes. For mild to moderate pain, especially that of primary dysmenorrhea, usual dosage is 400 mg every 4 to 6 hours as needed. The drug may be given with milk or food to minimize gastrointestinal side effects. *Ibuprofen* has been discussed in detail by Kaizer (1979) and by Adams and Buckler (in Symposium, 1983a).

Pharmacokinetics and Metabolism. *Ibuprofen* is rapidly absorbed after oral administration, and peak concentration

Table A-II-1
PHARMACOKINETIC DATA (Continued)

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE (ml·min ⁻¹ ·kg ⁻¹)	VOL. DIST. (liters/kg)	HAFLIFE (hours)	PEAK TIME (hours)	PEAK CONCENTRATIONS
HYDROMORPHONE* (Chapter 23)							
Oral: 42 ± 23 SC: ~80	6	7.1	14.6 ± 7.6	2.90 ± 1.31 ^b	2.4 ± 0.6	IV: 1.1 ± 0.2 ^c Oral: 1.1 ± 0.2 ^c	IV: 242 ng/ml ^c Oral: 11.8 ± 2.6 ng/ml ^c
<p>*Data from healthy male subjects. Extensively metabolized. The principal metabolite, 3-glucuronide, accumulates to much higher (21-464) levels than parent drug, and may contribute to some side effects (not antinociceptive).</p> <p>^bSee reported.</p> <p>^cFollowing a single 2-mg IV (bolus, sample at 3 minutes) or 4-mg oral dose.</p>							
HYDROXYUREA^{1,2} (Chapter 52)							
108 ± 18 (79-108)	35.8 ± 14.2	Negligible	72 ± 17 ml·min ⁻¹ (m ²) ^{-1b} (36.2-72.5)	19.7 ± 4.6 lit ²	3.4 ± 0.7 (2.8-4.5)	IV: 0.5 ^c Oral: 1.2 ± 1.2 ^c	IV: 1007 ± 371 μM ^c Oral: 794 ± 241 μM ^c
<p>¹Data from male and female patients treated for solid tumors. A range of mean values from multiple studies is shown in parentheses.</p> <p>²Nominal elimination of hydroxyurea is thought to exhibit saturable kinetics through a 10- to 30-mg/kg dose range.</p> <p>^cFollowing a single 2-g 3D-uridine intravenous infusion or oral dose.</p>							
IBUPROFEN* (Chapter 27)							
80	<1	>99 ^b ↔ RA, Alb	0.75 ± 0.20 ^{bc} ↑ CF ↔ Child, RA	0.15 ± 0.02 ^c ↑ CF	2 ± 0.5 ^d ↔ RA, CF, Child ↑ Cur	1.6 ± 0.3 ^d	61.1 ± 5.5 μg/ml ^d
<p>*Racemic mixture. Kinetic parameters for the active S-(+)-enantiomer do not differ from those for the inactive R-(-)-enantiomer when administered separately; 63 ± 6% of the R-(-)-enantiomer undergoes conversion to the active form.</p> <p>^bUnbound percent of S-(+)-ibuprofen (0.77 ± 0.20%) is significantly greater than that of R-(-)-ibuprofen (0.45 ± 0.06%). Binding of each enantiomer is concentration dependent and is influenced by the presence of the optical isotope, leading to nonlinear elimination kinetics.</p> <p>^cCL/F and V_{d/F} reported.</p> <p>^dFollowing a single 800-mg dose of racemate. A level of 10 μg/ml provides antipyresis in febrile children.</p>							

References: Hagen, N., Thirwell, M.P., Dhalluin, H.S., Rahul, N., Hacsanyi, Z., and Dukes, A.C. Steady-state pharmacokinetics of hydromorphone and hydromorphone-3-glucuronide in cancer patients after immediate and controlled-release hydromorphone. *J. Clin. Pharmacol.* 1995; 35:37-44.

Moulin, D.E., Kress, J.R., Murray-Pascoe, N., and Bouquillon, A.J. Comparison of continuous subcutaneous and intravenous hydromorphone infusions for management of cancer pain. *Lancet* 1991; 337:465-468.

Pezak, P.V., Ritschel, W.A., Coyte, D.E., Gregg, R.V., and Denson, D.D. Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. *Biopharm. Drug Dispos.* 1988; 9:183-199.

References: Gwill, P.R., and Traversell, W.G. Pharmacokinetics and pharmacodynamics of hydroxyurea. *Clin. Pharmacol.* 1998; 34:347-353.

Rodriguez, G.J., Kohn, J.G., Weiss, G.R., Hilsenbeck, S.G., Eckardt, J.R., Thurman, A., Rinaldi, D.A., Hodges, S., Vos Hoff, D.D., and Kowinsky E.K. A bioavailability and pharmacokinetic study of oral and intravenous hydroxyurea. *Blood* 1998; 91:1533-1541.

References: Lee, E.J., Williams, K., Day, R., Graham, G., and Changpin, D. Stereoselective disposition of ibuprofen enantiomers in man. *Br. J. Clin. Pharmacol.* 1985; 19:669-674.

Lockwood, O.F., Albert, K.S., Gillespie, W.R., Bock, G.O., Harbison, T.M., Sautter, G.J., and Wayne, J.T. Pharmacokinetics of ibuprofen in man. I. Free and total enantiomer relationships. *Clin. Pharmacol. Ther.* 1983; 34:97-103.

BEST AVAILABLE COPY